Clinical guidelines for the treatment of hepatitis C in Iceland

For the **Treatment as Prevention for Hepatitis C in Iceland (TraP Hep C)**

A nationwide campaign for reducing disease burden using combination antiviral treatment

Whom to treat

All patients infected with the hepatitis C virus should be considered for treatment. An eligible case of chronic hepatitis C infection is defined by two separate positive HCV PCR tests obtained at least 3 months apart. Patients who actively inject drugs and have high risk of transmitting disease and have one positive PCR will be considered for treatment as well.
Children age 16-18 may be considered for treatment.

Highest priority for treatment

A. Highest risk for progression to cirrhosis or severe complications
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4/transient elastography>12.5 kPa)
Organ transplant: pre- or post liver transplantation
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
HIV-1 coinfection and moderate fibrosis (Metavir 2)
Hepatitis B virus (HBV) coinfection and moderate fibrosis (Metavir 2)

B. Persons at Elevated risk of HCV transmission and in whom HCV treatment may yield transmission reduction benefits
Active injection drug users
Incarcerated persons

Absolute contraindications for treatment

Imminent risk of death (within 6 months) due to serious comorbid diseases as judged by the treating physicians
Pregnancy, breastfeeding or plans to become pregnant

Treatment regimens

First choice - Sofosbuvir/Velpatasvir (SOF/ VEL)

The first choice of treatment regimen for all genotypes is a fixed dose combination with sofosbuvir and velpatasvir.

Sofosbuvir (SOF) is a nucleotide NS5B inhibitor that was approved in the EU in November 2013 and in the USA in December 2013. Velpatasvir is a new pangenotypic HCV NS5A inhibitor with antiviral activity against HCV replicons in genotypes 1 through 6. Velpatasviris only available in a fixed dose combination with SOF (SOF 400mg/VEL 100 mg) in a product named Epclusa® which was approved in the EU in 2016. Epclusa® is given as a single pill once daily with or without food. Treatment duration is 12 weeks. Some patients with genotype 3 HCV infection who have compensated cirrhosis, and patients of all genotypes with decompensated cirrhosis may benefit from the addition of ribavirin (RBV) along with SOF/VEL. When used in combination with ribavirin, refer to the Summary of Product Characteristics of ribavirin. In patients with decompensated cirrhosis, ribavirin should be administered at a starting dose of 600 mg given in a divided daily dose. If the starting dose is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg). If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels.

Efficacy, side effects and duration of treatment with SOF/VEL.

In a recent double-blind, placebo-controlled study (ASTRAL-1)involving untreated and previously treated patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection, including those with compensated cirrhosis, 99% of patients achieved sustained virological response at 12 weeks post treatment (SVR12)[1]. In the ASTRAL-3 study, among patients with HCV genotype 3, the rate of sustained virologic response was 95%, including 97% and 91% for non cirrhotic and cirrhotics respectively[2]. The SVR for treatment experienced non cirrhotic genotype 3 patients was 91%. The overall rates of SVR12 in patients with decompensated cirrhosis treated in the ASTRAL-4 study were 83% among patients who received 12 weeks of SOF/VEL compared to 94% among those who received 12 weeksof SOF/VEL plus ribavirin[3]. Patients with decompensated cirrhosis are generally more difficult to treat, have lower SVR, and may benefit from the addition of ribavirin to the treatment regimen.

Most side effects from SOF/VEL are mild, with headache , fatigue, nausea, and nasopharyngitis being the most common. RBV, which may be used in some patients along with SOF/VEL , causes

[1] Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015;373:2599-607.

[2] Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015; 373:2608-17.

[3]Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618-28.

anemia that is usually treated with dose reduction. RBV also has teratogenic effects and female study participants who receive RBV should not conceive for the duration of the study and for six months after the treatment has stopped. Male patients who receive RBV should not father a child or donate sperm for the treatment period and the following six months. The current package insert should be consulted prior to initiation of therapy.

Initial treatment regimens:

GT1,2,3,4,5,6		
TN, TE, cirrhotic, noncirrhotic (a)	SOF/VEL	12 weeks
Decompensated cirrhosis	SOF/VEL+RBV	12 weeks (24 weeks if no RBV)

a. For GT3 infected patients with compensated cirrhosis and TE non cirrhotic GT3 infected patients, ribavirin should be added if there is no contraindication or intolerance.

Table 1. Initial treatment regimens for chronic HCV in Iceland.

Legends: TN: treatment-naïve; TE: treatment-experienced.

Treatment of patients who did not not achieve SVR with treatment with LDV/SOF+/-RBV:

GT3	SOF/VEL	12 weeks
GT1	SOF/VEL+RBV	24 weeks or wait for new DAAs

Table 2. Treatment of patients who did not not achieve SVR with treatment with LDV/SOF+/-RBV

Relative contraindication for treatment/contraindication for SOF/VEL.

For contraindications, precautions and drug interactions guidance should be sought by the European Medicines Agency SmPC most current recommendations.

SOF/VEL is contraindicated in patients receiving potent P-glycoprotein (P-gp) or potent cytochrome P450 (CYP) inducers. SOF/VEL is contraindicated in patients receiving phenytoin, carbazepine, rifampicin, rifabutin or St John´s Wort. As concomitant use of SOF/VEL with amoidarone can result in severe bradycardia these drugs should only be used concomitantly if there are no other alternative anti-arrythmic treatments. Patients will be informed of potential drug interactions and offered treatment modifications or deferral of HCV treatment until it becomes feasible as determined by the patient´s physician.

The safety of SOF/VEL has not been assessed in patients with severe renal impairment [eGFR] < 30 ml/mín./1,73 m2 or end stage renal disease requiring hemodialysis.

Second choice - Alternative treatment regimens to consider for patients who have contraindications for SOF/VEL.

GT 1a/1b

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) (Viekirax®) plus twice-daily dosed dasabuvir (250 mg) (Exviera®)for 12 or 24 weeks plus or minus weight-based RBV depending on the presence or absence of cirrhosis, viral subtype and previous treatment history.

or

Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks.

or

Daily daclatasvir (60 mg*) (Daklinza®)and sofosbuvir (400 mg) (Sovaldi®)for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) (cirrhosis).

GT 2

Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks.

GT 3

Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis). Depending on the presence or absence of cirrhosis and previous treatment history.

or

Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks.

GT 4

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis).

or

Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks.

GT 5 or 6

There are no cases of these genotypes in Iceland, if encountered they should be treated following consultation with the coordinators of the nationwide campaign.

Recommended screening and monitoring strategy for patients who are starting hepatitis C treatment, are on treatment, or have completed therapy.

At an initial, baseline visit the following blood tests will be performed: CBC, , creatinine, ALAT, ASAT, bilirubin, albumin, INR, HCV RNA by PCR (quantitative, "viral load"), HCV genotyping (unless already genotyped since 2009), HBsAg, anti-HBc, HIV ab. For female patients of childbearing age, pregnancy test should be performed. Hepatic elastography will be performed unless an elastography or a liver biopsy has been performed within the preceding 6 months. An interview should be performed where the patients risk for transmitting the hepatitis C virus is assessed and recorded. The results of these laboratory tests, elastography, and interview are used to assess the need for therapy.

If a subject qualifies for treatment they will start the indicated treatment program as per these guidelines within 4 weeks. Following a treatment initiation visit at week 0, clinic visits will be at week 2 (for patients receiving ribavirin), 4, 8, 12, 16, 20, 24, and 36 depending on the length of treatment. Patients deemed at high risk of transmitting disease may have their treatment initiation visit on the same day as their screening visit.

Patients who have positive serologic tests for HBV: HBsAg positive: Measure HBV DNA at baseline, EOT, 12 weeks and 24 weeks post treatment, in addition to ALAT and ASAT.
HBsAg negative, anti-HBc positive: No additional testing.
At clinic visit week 2 (patients receiving ribavirin) CBC will be measured. At all other clinic visit the following tests will be performed: CBC, creatinine, ALAT and bilirubin. For female patients of childbearing age receiving RBV, pregnancy test should be performed at each visit. Quantitative HCV RNA by PCR will be performed at the end of treatment and at 12 weeks post treatment (at 8, 12, 20, 24, and 36 weeks depending on length of treatment). SVR is defined as negative HCV RNA PCR 12 weeks post treatment (SVR12). These recommendations represent the minimum amount of monitoring, but if more close monitoring is deemed necessary (such as for patients with cirrhosis) by the treating physician, additional visits should be planned. For patients who are at risk for poor compliance such as active drug users, special measures, such as more frequent clinic visits will be implemented.
Patients who do not respond to therapy or relapse (positive PCR) after end of treatment should be tested for NS5A RAVs (resistance associated variants). For those who are PCR negative at the end of treatment but positive at 12 weeks post treatment or thereafter and may have been re-exposed to the virus, phylogenetic analysis should be performed to determine if there is reinfection or relapse.
Patients with who do not acheive SVR will need continued follow up with office visits every 6 months.
Patients with cirrhosis will need continued monitoring every 6 months regardless of response to therapy to evaluate for development of HCC and/ or decomensation.
Patients with significant fibrosis (Metavir F3 or transient elastography >11.0 kPa) who achieve SVR should be followed with yearly clinic visits for 5 years.

December 2016

Sigurður Ólafsson MD, FACP, Director of Hepatology, Landspitali

Magnús Gottfreðsson MD, PhD, FACP, Infectious diseases/Department of scientific affairs, Landspitali

Einar St. Björnsson MD, Chief of Gastroenterology and Hepatology, Landspitali

Þorvarður Löve MD, PhD, Rheumatologist, Landspitali

Óttar M. Bergmann MD, Gastroenterologist/Hepatologist, Landspitali

Valgerður Rúnarsdóttir MD, Addiction medicine, SÁÁ treatment center